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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,435	02/15/2002	M. Vijay Kumar	M0351-268908	3474

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,435	KUMAR, M. VIJAY	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,16-22,25,26,28-38,42,43 and 45-52* is/are pending in the application.

4a) Of the above claim(s) *2-12, 16-22, 25-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-38,42,43 and 45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 28-38, 42-43, 45-52 are examined in the instant application.

The following are the remaining rejections.

REJECTION UNDER 35 USC 103

Claims 28-38, 42-43, 45-52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999, Intl J Oncology, 15(4): 793-802, of record, in view of Yu et al, 2000, Cancer Res, 60: 2384-2389, IDS # 128, submitted on 11/12/02, or Gliniak B et al, 1999, Cancer Res, 59 (24): 6153-6158, and further in view of Fathy El Etreby et al, 2000, The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02, or Koide SS et al, J Reproductive Medicine, 1998, 43(7): 551-560, IDS # 53, submitted on 11/12/02, for reasons already of record in paper 09/09/05.

A. Applicant argues that nothing in the references alone or in combination teaches or suggests the combination of TRAIL and an antiprogestin, such as Mifepristone as a chemotherapeutic composition. Applicant argues that nothing in the references alone or in combination teaches or suggests that the combination of TRAIL and an antiprogestin would be effective in treating prostate cancer cells that are refractory to either TRAIL or an antiprogestin, or that said combination would be more effective than the additive effect of the TRAIL and the antiprogestin separately applied to cancer cells.

Applicant argues that Bonavida teaches away from the claimed invention, as one would be discouraged from using a second agent of the TRAIL pathway in combination with TRAIL. Applicant argues that thus Bonavida suggest the use of TRAIL in combination with cyclohexamide (an inhibitor of protein translation), adriamycin (an antibiotic) or actinomycin D (a terminator of transcription). Applicant argues that Bonavida describes using TRAIL with chemotherapeutics that work by different and more generalized biochemical pathway, e.g., actinomycin D, adriamycin, and cyclohexamide. Applicant argues that Bonavida suggests the use of compounds that can prevent the development of anti-apoptotic cellular machinery as a means to overcome the resistance to TRAIL (p.797, column 1). Applicant argues that Gliniak describes the use of TRAIL in combination with a topoisomerase inhibitor to treat colon cancer. Applicant argues that Gliniak specifically notes that combining TRAIL with many chemotherapeutic agents, including cisplatin, 5-FU, mitomycin, etopside or adriamycin did not result in enhancement of cytotoxicity. Applicant argues that thus reading Gliniak, one would be discouraged from using most chemotherapeutic agents in combination with TRAIL.

Applicant argues that Yu describes that TRAIL can induce cell death in certain androgen-insensitive prostate cancer cells. Applicant argues that, like Bonavida and Gliniak, Yu does not describe or suggest a mechanism by which antiprogestin would be able to increase the effectiveness of TRAIL, so as to provide greater than additive effect for the induction of cell death.

Applicant's arguments in paper of 02/08/06 have been considered but are not found to be persuasive for the following reasons:

Bonavida teach that two strategies can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis, one is the suppression of anti-apoptotic molecule, another is the up-regulation of pro-apoptotic molecule (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization). Bonavida teaches that conventional chemotherapy does not simply prevent cell replication, but in many cases induces a process of programmed cell death (p.800, second column, lines 2-4), and that for example, Actinomycin D, a drug that inhibits RNA synthesis, also decreases the expression of Bcl-XL (a death inhibitor or anti-apoptotic protein) (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization). Bonavida teaches that the addition of cyclohexamide, or actinomycin D, or Doxorubin (Adriamycin) reverse various cancer cells that are resistant to TRAIL-mediated apoptosis, including prostate cancer (p.797, first column, item 6 to p.799).

Thus, contrary to Applicant's arguments, Bonavida does not teach away from the claimed invention. The chemotherapeutic drugs taught by Bonavida, all are similar to TRAIL, in that they also effect the apoptotic pathway, and it would have been obvious to use the strategies of Bonavida et al to treat cancers, including prostate cancers, by using a compound that either suppresses an anti-apoptotic molecule, or up-regulates a pro-apoptotic molecule, such as an antiprogestin or Mifepristone, the anti- tumor action of which is mediated via the progesterone receptor, and related to induction of apoptosis, as taught by Fathy El Etreby et al.

In addition, although Gliniak teaches that combining TRAIL with many chemotherapeutic agents, including cisplatin, 5-FU, mitomycin, etopside or adriamycin did not result in enhancement of cytotoxicity, Gliniak teaches mechanism of action of compounds that do synergize with TRAIL. That is Gliniak teaches that in a manner similar to actinomycin D, and cyclohexamide, campthothecin, an inhibitor of topoisomerase I, synergizes with TRAIL, by ultimately inhibiting the synthesis of an apoptosis-regulatory protein (p.6158, first column). Thus the teaching of Gliniak et al reinforces the strategies taught by Bonavida. From the teaching of Gliniak, one would choose among various chemotherapeutic agents those that inhibit the synthesis of an apoptosis-regulatory protein to enhance cytotoxicity.

Further, although Gliniak et al teach treating colon cancer in vivo, Gliniak et al also teach that TRAIL can induce apoptosis in a variety of cancers in vitro, and that the in vivo sensitivity of TRAil in colon cancer parallels their susceptibility to TRAIL-induced apoptosis in vitro.

Concerning Applicant's arguments that, like Bonavida and Gliniak, Yu does not describe or suggest a mechanism by which antiprogestin would be able to increase the effectiveness of TRAIL, so as to provide greater than additive effect for the induction of cell death, it is noted that the claims are drawn to a composition, mechanism by which antiprogestin would be able to increase the effectiveness of TRAIL is not germane, and the limitation of treating prostate cancer with a synergistic effect is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The Claims 28-38, 42-43, 45-52 read on the ingredient per se,

which is a composition comprising a TRAIL polypeptide and antiprogestin or Mifepristone.

In addition, although the references do not specifically teach that the combination of TRAIL and antiprogestin or Mifepristone would have a synergistic effect, however, the claimed composition appears to be the same as the composition taught by the combined prior art , absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

B. Applicant argues that Koide does not add to the deficiencies of Bonavida, Gliniak and Yu. Applicant argues that Koide describe the use of Mifepristone for treatment of cancers other than prostate cancer. Applicant argues that Koide teaches away from Applicant's finding that Mifespristone acts on the TRAIL pathway to sensitize cells to TRAIL, because Koide suggests that Mifepristone acts in a competitive manner with ligands for the progesterone receptor.

Applicant's arguments in paper of 02/08/06 have been considered but are not found to be persuasive for the following reasons:

Koide was recited to show that various cancers could be treated by Mifepristone, which acts via progesterone receptor, a different mechanism than that of TRAIL, thus reinforcing the teaching of Fathy El Etreby et al that the antitumor action of antiprogestins is mediated via the progesterone receptor, and related to induction of apoptosis.

Further, whether Mifespristone acts on the TRAIL pathway to sensitize cells to TRAIL is not german, because the claims are drawn to a composition, and not a method.

C. Applicant argues that although El Etreby teaches that Mifepristone exhibits anti-tumor activity in androgen-sensitive and androgen-insensitive prostate cancer cells, El Etreby does not describe or suggest that Mifepristone or other antiprogestins may be used to increase the TRAIL sensitivity of androgen-sensitive cancer cells, such as LNCaP cells, or that compositions having this ability may be clinically important. Applicant asserts that thus El Etreby, in combination with Bonavida, Gliniak, Yu or Koide do not describe the Mifepristone may act in a synergistic manner with TRAIL, at the level of the TRAIL pathway, because Mifespristone acts via the progesterone receptor.

Applicant argues that the formulation of a composition of TRAIL and an antiprogestin to provide a composition with increased efficacy is not an intended use, but a quality of the composition itself that renders the composition as a chemotherapeutic agent that provides surprising advantage over composition of the prior art.

Applicant argues that Applicant's methods maintain specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway, and that this is in constrast with the agents proposed by Bonavida and Gliniak, which act by much more generalized mechanisms to induce cell death, and thus can result in non-specific side effects. Applicant argues that this is also in contrast to the studies of El Etreby, which suggest that Mifepristone may act to overcome the apoptosis resistance of androgen-independent cells.

Applicant argues that Gliniak, Koide, Yu, and El Etreby do not teach the use of TRAIL with another agent for treating prostate cancer.

Applicant argues that the prior art only provides an invitation to explore.

Applicant's arguments in paper of 02/08/06 have been considered but are not found to be persuasive for the following reasons:

Fathy El Etreby et al teach that the antitumor action of antiprogestins is mediated via the progesterone receptor, and related to induction of apoptosis (p.100, first column, first paragraph).

Although Gliniak, Koide, Yu, and El Etreby do not describe or suggest that Mifepristone or other antiprogestins may be used to increase the TRAIL sensitivity of androgen-sensitive cancer cells, such as LNCaP cells, however, it would have been obvious to use a drug that also induces apoptosis, such as Mifepristone taught by El Etreby for use in combination with TRAIL, to replace a chemotherapeutic drug, such as actinomycin D, that suppresses an anti-apoptotic molecule, taught by Bonavida et al.

The reasons for such combination are as follows:

1) Using a drug that induces apoptosis in combination with TRAIL is one of the strageties suggested by Bonavida to sensitize cancer cells, including prostate cancer cells, that are resistant to TRAIL-mediated apoptosis. Bonavida teach that two strategies can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis, one is the suppression of anti-apoptotic molecule, another is the up-regulation of pro-apoptotic molecule (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization).

Further, Mifepristone has an advantage that it could be used as an adjuvant therapeutic agent in cancers, such a unresectable meningioma, and leiomyoma, that are refractory to chemotherapy, with a marked alleviation of pain as taught by Koide (p.551, Study design).

Moreover, Mifepritone is suggested to be used only in combination with another agent, as taught by Koide (p.551, Study design).

2) An antiprogestin, such as Mifestrone, would affect apoptosis by a different mechanism than TRAIL, via the prosgesterone receptor, as taught by Fathy El Etreby et al, and and Koide, and thus would be complementary to TRAIL and would increase the chance of killing cancer cells, especially those that are resistant to TRAIL.

3) An antiprogestin, such as Mifestrone, taught by Fathy El Etreby et al would be complementary to TRAIL in treating prostate cancer, because Mifestrone et al could kill both androgen-sensitive and androgen-insensitive prostate cancer cells, as taught by Fathy El Etreby et al.

Concerning Applicant's arguments that the quality of the composition itself that renders the composition as a chemotherapeutic agent that provides surprising advantage over composition of the prior art, it is noted that the composition taught by the combined prior art seems to be the same as the claimed composition.

Although the references do not specifically teach that the combination of TRAIL and an antiprogestin or Mifepristone would have a synergistic effect, however, the claimed composition appears to be the same as the composition taught by the combined prior art , absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Concerning Applicant's argument that Applicant's methods maintain specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway, and that this is in constrast with the agents proposed by Bonavida and Gliniak, and also in contrast to the studies of El Etreby, which suggest that Mifepristone may act to overcome the apoptosis resistance of androgen-independent cells, it is noted that the instant claims are drawn to a composition claim and not a method claim, and the

composition taught by the combined art seems to be the same as the claimed composition, surpra, and thus the arguments are moot.

One would have been motivated to make a composition comprising TRAIL and an antiprogestin or Mifepristone with a reasonable expectation of success, for use in treating cancer cells, including prostate cancer cells that are resistant to TRAIL, because Mifepristone would kill all different types of cancer cells, including prostate cancer cells, whether it is androgen-sensitive or -insensitive cells, as taught by El Etreby, and Koide, and because Mifepristone is complementary to TRAIL, and induces apoptosis of cells by a different mechanism than that of TRAIL.

D. Secondary consideration

Applicant submits a Declaration by Dr. M V Kumar.

The Declaration discloses that the synergistic effect to reduce tumor cell survival by Mifepristone is an unexpected result. The Declaration discloses that the finding that Mifepristone could act on the TRAIL pathway to sensitize cells to TRAIL is also unexpected. The Declaration also discloses that the instant application fulfills a long-felt need for treating both hormone-sensitive and hormone-insensitive cells to induce apoptosis.

The submission of the Declaration by Dr. M V Kumar is acknowledged and entered.

The Examiner takes noted that although the references do not specifically teach that the combination of TRAIL and an antiprogestin or Mifepristone would have a synergistic effect, or that Mifepristone could act on the TRAIL pathway to sensitize cells

to TRAIL, however, the claimed composition appears to be the same as the composition taught by the combined prior art , absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Further, the limitation of treating prostate cancer with a synergistic effect is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The Claims 28-38, 42-43, 45-52 read on the ingredient per se, which is a composition comprising a TRAIL polypeptide and antiprogestin or Mifepristone

In addition, since the claims are composition claims, the mechanism of action of Mifepristone, i.e. whether Mifepristone could act on the TRAIL pathway to sensitize cells to TRAIL is not germane.

REJOINDER OF WITHDRAWN CLAIMS

Applicant argues that the withdrawn method claims have been amended to include the limitation of the product claims, and thus should be rejoined with the pending composition claims.

The Examiner takes note that although at the time of allowance, rejoining the method claims having all the limitation of the product claims with the product claims is a matter of right for Applicant, the pending composition claims however are presently not allowable. The consideration of rejoining the method claims with the composition claims would be made only at the time of allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

MINH TAM DAVIS

April 12, 2006